WEST Search History

DATE: Tuesday, March 19, 2002

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=OR		
L20	L18 and l5	0	L20
L19	L18 and L6	0	L19
L18	combretastatin	56	L18
L17	L14 and L6	0	L17
L16	L15 and L6	0	L16
L15	L14 and l6	0	L15
L14	ca-4	50	L14
L13	l6 and "tumor vasculature"	4	L13
L12	l6 and "vascular damaging agent?"	0	L12
L11	L6 and angiogensis	0	L11
L10	L6 and colchinol?	0	L10
L9	L6 and ca4p	0	L9
L8	L6 and 2-amino-4-methylpyridine	5	L8
L7	L6 and combretastatin?	0	L7
L6	L5 and inhibitor?	251	L6
L5	L4 and "no synthase"	312	L5
L4	nitric oxide synthase	461249	L4
L3	"(no or nitric oxide) synthase"	0	L3
L2	L1 and "(NO or nitric oxide) synthase?"	0	L2
L1	(NO or nitric oxide)synthase?	2438719	L1

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 5 of 5 returned.

☐ 1. Document ID: US 6071906 A

L8: Entry 1 of 5 File: USPT Jun 6, 2000

US-PAT-NO: 6071906
DOCUMENT-IDENTIFIER: US 6071906 A

TITLE: Imidino piperidine derivatives useful as nitric oxide synthase inhibitors

DATE-ISSUED: June 6, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hansen, Jr.; Donald W.	Skokie	IL		
Currie; Mark G.	St. Charles	MO		
Hallinan; E. Ann	Evanston	IL		
Fok; Kam F.	St. Louis	MO		
Hagen; Timothy J.	Manchester	MO		
Bergmanis; Arija A.	Des Plaines	IL		
Kramer; Steven W.	Des Plaines	IL		
Lee; Len F.	St. Charles	MO		
Metz; Suzanne	Chesterfield	MO		
Moore; William M.	St. Charles	MO		
Peterson; Karen B.	Vernon Hills	IL		
Pitzele; Barnett S.	Skokie	IL		
Spangler; Dale P.	Deerfield	IL		
Webber; R. Keith	St. Peters	MO		
Toth; Mihaly V.	St. Louis	MO		
Trivedi; Mahima	Glenview	IL		
Tjoeng; Foe S.	Manchester	MO		

US-CL-CURRENT: 514/227.2; 546/242, 546/244

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6046211 A

L8: Entry 2 of 5 File: USPT Apr 4, 2000

US-PAT-NO: 6046211
DOCUMENT-IDENTIFIER: US 6046211 A

TITLE: Amidino derivatives useful as nitric oxide synthase inhibitors

DATE-ISSUED: April 4, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hansen, Jr.; Donald W.	Skokie	IL		
Currie; Mark G.	St. Charles	MO		
Hallinan; E. Ann	Evanston	IL		
Fok; Kam F.	St. Louis	MO		
Hagen; Timothy J.	Manchester	MO		
Bergmanis; Arija A.	Des Plaines	IL		
Kramer; Steven W.	Des Plaines	IL		
Lee; Len F.	St. Charles	MO		
Metz; Suzanne	Chesterfield	MO		
Moore; William M.	St. Charles	MO		
Peterson; Karen B.	Vernon Hills	IL		
Pitzele; Barnett S.	Skokie	IL		
Spangler; Dale P.	Deerfield	IL		
Webber; R. Keith	St. Peters	MO		
Toth; Mihaly V.	St. Louis	MO		
Trivedi; Mahima	Glenview	IL		
Tjoeng; Foe S.	Manchester	MO		

US-CL-CURRENT: 514/310; 514/217.11, 514/224.2, 514/230.5, 514/258.1, 514/309, 514/312, 514/313, 544/253, 544/47, 544/48 , 544/50, 544/90, 544/91, 544/92, 546/113, 546/141, 546/143, 546/153, 546/159

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 3. Document ID: US 5972975 A

L8: Entry 3 of 5 File: USPT Oct 26, 1999

US-PAT-NO: 5972975
DOCUMENT-IDENTIFIER: US 5972975 A

TITLE: Substituted 2-aminopyridines as inhibitors of nitric oxide synthase

DATE-ISSUED: October 26, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Esser; Craig	Rahway	NJ		
Hagmann; William	Rahway	NJ		
Hoffman; William	Rahway	NJ		
Shah; Shrenik	Rahway	NJ		
Wong; Kenny	Rahway	NJ		
Chabin; Renee	Rahway	NJ		
Guthikonda; Ravindra	Rahway	NJ		
Maccoss; Malcolm	Rahway	NJ		
Caldwell; Charles	Rahway	NJ		
Durette; Philippe	Rahway	NJ		

US-CL-CURRENT: 514/352; 514/211.08, 514/211.15, 514/217.06, 514/217.07, 514/217.08, 514/217.09, 514/218, 514/224.2, 514/226.5, 514/226.8, 514/228.2, 514/228.5, 514/230.5, 514/233.8, 514/234.2, 514/234.5, 514/248, 514/249 , 514/255.05, 514/256, 514/269, 514/299, 514/300, 514/301, 514/302, 514/303, 514/307, 514/310, 514/311, 514/313, 514/314, 514/334, 514/344, 514/346, 514/349, 540/544, 540/553, 540/575, 540/597, 544/105, 544/119, 544/127, 544/236, 544/238, 544/277, 544/279, 544/333, 544/350, 544/405, 544/48, 544/55, 544/61, 544/91, 544/96, 546/112, 546/113, 546/114, 546/115, 546/118, 546/119, 546/122, 546/143, 546/159, 546/257 , 546/289, 546/292, 546/297, 546/304, 546/307, 546/308, 546/311

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments

KWIC | Draw Desc | Image

☐ 4. Document ID: US 5908842 A

L8: Entry 4 of 5 File: USPT Jun 1, 1999

US-PAT-NO: 5908842
DOCUMENT-IDENTIFIER: US 5908842 A

TITLE: Substituted 2-acylamino-pyridines as inhibitors of nitric oxide synthase

DATE-ISSUED: June 1, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Guthikonda; Ravindra	Rahway	NJ		
Hagmann; William	Rahway	NJ		
Maccoss; Malcolm	Rahway	NJ		
Shah; Shrenik	Rahway	NJ		
Durette; Philippe	Rahway	NJ		

US-CL-CURRENT: 514/253.01; 514/231.5, 514/252.03, 514/253.04, 514/253.05, 514/253.06, 514/299, 514/300, 514/301, 514/310 , 514/313, 514/353, 544/105, 544/350, 544/360, 546/112, 546/113, 546/114, 546/143, 546/159, 546/306

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments

KWIC | Draw Desc | Image

☐ 5. Document ID: US 5854234 A

L8: Entry 5 of 5 File: USPT Dec 29, 1998

US-PAT-NO: 5854234
DOCUMENT-IDENTIFIER: US 5854234 A

TITLE: Amidino dervatives useful as nitric oxide synthase inhibitors

DATE-ISSUED: December 29, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hansen, Jr.; Donald W.	Skokie	IL		
Currie; Mark G.	St. Charles	MO		
Hallinan; E. Ann	Evanston	IL		
Fok; Kam F.	St. Louis	MO		
Hagen; Timothy J.	Manchester	MO		
Bergmanis; Arija A.	Des Plains	IL		
Kramer; Steven W.	Des Plains	IL		
Lee; Len F.	St. Charles	MO		
Metz; Suzanne	Chesterfield	MO		
Moore; William M.	St. Charles	MO		
Peterson; Karen B.	Vernon Hills	IL		
Pitzele; Barnett S.	Skokie	IL		
Spangler; Dale P.	Deerfield	IL		
Webber; R. Keith	St. Peters	MO		
Toth; Mihaly V.	St. Louis	MO		
Trivedi; Mahima	Glenview	IL		
Tjoeng; Foe S.	Manchester	MO		

US-CL-CURRENT: 514/211.01; 514/183, 514/217.11, 514/218, 514/227.2, 514/228.8, 514/256, 514/329, 514/370, 514/377, 514/386, 514/426, 540/467, 540/470, 540/480, 540/481, 540/482, 540/544, 540/553, 540/596, 540/598, 540/601, 540/602, 540/603, 540/604, 540/605, 540/606

Terms	Documents
L6 and 2-amino-4-methylpyridine	5

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Search Results - Record(s) 1 through 4 of 4 returned.

☐ 1. Document ID: US 6020308 A

L13: Entry 1 of 4 File: USPT Feb 1, 2000

US-PAT-NO: 6020308
DOCUMENT-IDENTIFIER: US 6020308 A

TITLE: Methods for improving therapeutic effectiveness of treatment of vascularization disorders

DATE-ISSUED: February 1, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dewhirst; Mark W.	Chapel Hill	NC		
Meyer; Robert E.	Cary	NC		
Bonaventura; Joseph	Beaufort	NC		
DeAngelo; Joseph	Hamtramck	MI		

US-CL-CURRENT: 514/6; 514/12, 514/561, 514/565, 514/832, 514/833, 514/929, 514/930, 530/385

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 2. Document ID: US 5788958 A

L13: Entry 2 of 4 File: USPT Aug 4, 1998

US-PAT-NO: 5788958
DOCUMENT-IDENTIFIER: US 5788958 A

TITLE: Methods for improving therapeutic effectiveness of agents for the treatment of solid tumors and other disorders

DATE-ISSUED: August 4, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dewhirst; Mark W.	Chapel Hill	NC		
Meyer; Robert E.	Cary	NC		
Bonaventura; Joseph	Beaufort	NC		
DeAngelo; Joseph	Hamtramck	MI		

US-CL-CURRENT: 424/78.38; 424/85.2, 514/12, 514/561, 514/564, 514/6, 514/723, 562/553, 562/560

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 3. Document ID: US 5612310 A

L13: Entry 3 of 4 File: USPT Mar 18, 1997

US-PAT-NO: 5612310
DOCUMENT-IDENTIFIER: US 5612310 A

TITLE: Methods for improving therapeutic effectiveness of agents for the treatment of solid tumors and other disorders

DATE-ISSUED: March 18, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dewhirst; Mark W.	Chapel Hill	NC		
Meyer; Robert E.	Cary	NC		
Bonaventura; Joseph	Beauford	NC		
DeAngelo; Joseph	Hamtramck	MI		

US-CL-CURRENT: 514/6; 514/832, 514/833

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 4. Document ID: US 5554638 A

L13: Entry 4 of 4 File: USPT Sep 10, 1996

US-PAT-NO: 5554638
DOCUMENT-IDENTIFIER: US 5554638 A

TITLE: Methods for improving therapeutic effectiveness of agents for the treatment of solid tumors and other disorders

DATE-ISSUED: September 10, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dewhirst; Mark W.	Chapel Hill	NC		
Meyer; Robert E.	Cary	NC		
Bonaventura; Joseph	Beaufort	NC		
DeAngelo; Joseph	Hamtramck	MI		

US-CL-CURRENT: 514/398; 514/411, 514/456, 514/551, 514/560, 514/565

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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Terms	Documents
16 and "tumor vasculature"	4

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1: Br J Cancer 2000 Sep;83(6):811-6 Related Articles, NEW Books, LinkOut

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IDEAL

Determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide.

Parkins CS, Holder AL, Hill SA, Chaplin DJ, Tozer GM.

Tumour Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, Middlesex, HA6 2JR, UK.

The anti-vascular action of the tubulin binding agent combretastatin A-4 phosphate (CA-4-P) has been quantified in two types of murine tumour, the breast adenocarcinoma CaNT and the round cell sarcoma SaS. The functional vascular volume, assessed using a fluorescent carbocyanine dye, was significantly reduced at 18 h after CA-4-P treatment in both tumour types, although the degree of reduction was very different in the two tumours. The SaS tumour, which has a higher nitric oxide synthase (NOS) activity than the CaNT tumour, showed approximately 10-fold greater resistance to vascular damage by CA-4-P. This is consistent with our previous findings, which showed that NO exerts a protective action against this drug. Simultaneous administration of CA-4-P with a NOS inhibitor, N(omega)-nitro-L-arginine (L-NNA), resulted in enhanced vascular damage and cytotoxicity in both tumour types. Administration of diethylamine NO, an NO donor, conferred protection against the vascular damaging effects. Following treatment with CA-4-P, neutrophil infiltration into the tumours, measured by myeloperoxidase (MPO) activity, was significantly increased. Levels of MPO activity also correlated with the levels of vascular injury and cytotoxicity measured in both tumour types. Neutrophilic MPO generates free radicals and may therefore contribute to the vascular damage associated with CA-4-P treatment. MPO activity was significantly increased in the presence of L-NNA, suggesting that the protective effect of NO against CA-4-P-induced vascular injury may be, at least partially, mediated by limiting neutrophil infiltration. The data are consistent with the hypothesis that neutrophil action contributes to vascular injury by CA-4-P and that NO generation acts to protect the tumour vasculature against CA4-P-induced injury. The protective effect of NO is probably associated with an anti-neutrophil action. Copyright

Search for 09/890,989

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E DAVIS PETER DAVID/IN 25
E1        7    DAVIS PETER/IN
E2        1    DAVIS PETER BRIAN ANDREW/IN
E3       20 --> DAVIS PETER DAVID/IN
E4        1    DAVIS PETER GEORGE/IN
E5        5    DAVIS PETER W/IN
E6        1    DAVIS PETER WILLIAM/IN
E7        1    DAVIS PHIL/IN
E8        1    DAVIS PHILIP E/IN
E9        1    DAVIS PHILIP K/IN
E10       1    DAVIS PHILIP R/IN
E11       8    DAVIS PHILIP S/IN
E12       7    DAVIS PHILIP W/IN
E13       1    DAVIS PHILLIP/IN
E14       2    DAVIS PHILLIP K/IN
E15       1    DAVIS PUTNAM/IN
E16       2    DAVIS R F/IN
E17       1    DAVIS R F JR/IN
E18      14    DAVIS R H/IN
E19       3    DAVIS R MICHAEL/IN
E20       2    DAVIS R O E/IN
E21       2    DAVIS R S/IN
E22       1    DAVIS R W G/IN
E23       3    DAVIS R W JR/IN
E24       1    DAVIS RACHEL D/IN
E25       1    DAVIS RALPH/IN

=> S (E3) AND (CA4P AND L-NNA)
         20 "DAVIS PETER DAVID"/IN
          4 CA4P
    1199606 L
       1391 NNA
          5 NNAS
       1395 NNA
            (NNA OR NNAS)
       1016 L-NNA
            (L(W)NNA)
L1        0 ("DAVIS PETER DAVID"/IN) AND (CA4P AND L-NNA)

=> s L-nna and e3
    1199606 L
       1391 NNA
          5 NNAS
       1395 NNA
```

(NNA OR NNAS)
1016 L-NNA
(L(W)NNA)
20 "DAVIS PETER DAVID"/IN
L2 0 L-NNA AND "DAVIS PETER DAVID"/IN

s combretastatin?
L2 244 COMBRETASTATIN?

=> s l1 and l2
L3 0 L1 AND L2

=> s 2-amino-4-methylpyridine
7263347 2
822026 AMINO
39 AMINOS
822044 AMINO
(AMINO OR AMINOS)
4381553 4
8965 METHYLPYRIDINE
679 METHYLPYRIDINES
9246 METHYLPYRIDINE
(METHYLPYRIDINE OR METHYLPYRIDINES)
L4 313 2-AMINO-4-METHYLPYRIDINE
(2(W)AMINO(W)4(W)METHYLPYRIDINE)

=> s l2 and l4
L5 1 L2 AND L4

=> dis l5

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
AN 2000:592549 CAPLUS
DN 133:172166
TI Combinations for the treatment of diseases involving angiogenesis
IN Davis, Peter David
PA Angiogene Pharmaceuticals Ltd., UK
SO PCT Int. Appl., 18 pp.
SYSTEM:OS - DIALOG OneSearch
File 399:CA SEARCH(R) 1967-2002/UD=13612
(c) 2002 AMERICAN CHEMICAL SOCIETY
*File 399: Use is subject to the terms of your user/customer agreement.
RANK charge added; see HELP RATES 399.
File 94:JICST-EPlus 1985-2002/Feb W1
(c)2002 Japan Science and Tech Corp(JST)
*File 94: There is no data missing. UDs have been adjusted to reflect

the current months data. See Help News94 for details.

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   Set  Items  Description
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?s 2(w)amino(w)methylpyridine?
      1461781  2
       839595  AMINO
         5387  METHYLPYRIDINE?
   S1      52  2(W)AMINO(W)METHYLPYRIDINE?
?s combretastatin(w)a4(w)phosphate? or ca4p
          152  COMBRETASTATIN
         4170  A4
       304494  PHOSPHATE?
            8  COMBRETASTATIN(W)A4(W)PHOSPHATE?
            0  CA4P
   S2       8  COMBRETASTATIN(W)A4(W)PHOSPHATE? OR CA4P
?s s1 and s2
           52  S1
            8  S2
   S3       0  S1 AND S2
?s L(w)N(w)nitroarginine? or l-nna
       205033  L
       473865  N
          589  NITROARGININE?
            4  L(W)N(W)NITROARGININE?
            0  L-NNA
   S4       4  L(W)N(W)NITROARGININE? OR L-NNA
?s s4 and s2
            4  S4
            8  S2
   S5       0  S4 AND S2
?s colchinol?
   S6      13  COLCHINOL?
?s s6 and (s1 or s4)
           13  S6
           52  S1
            4  S4
   S7       0  S6 AND (S1 OR S4)
?s antitulin?
   S8       0  ANTITULIN?
?s methoxy(w)phenylamine?
        36258  METHOXY
         6464  PHENYLAMINE?
   S9       4  METHOXY(W)PHENYLAMINE?
?s (s6 or s8 or s2) and (s1 or s4)
           13  S6
```

0 S8
8 S2
52 S1
4 S4
S10 0 (S6 OR S8 OR S2) AND (S1 OR S4)
FILE 'CAPLUS' ENTERED AT 12:43:44 ON 19 MAR 2002
L1 244 S COMBRETASTATIN?
L2 29 S COLCHINOL?
L3 9492 S NO SYNTHASE?
L4 18104 S NITRIC OXIDE SYNTHASE?
L5 3 S (L1 OR L2) AND (L3 OR L4)
L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
AN 2001:659027 CAPLUS
DN 136:295
TI Mechanisms associated with tumor vascular shut-down induced by combretastatin A-4 phosphate: intravital microscopy and measurement of vascular permeability
AU Tozer, Gillian M.; Prise, Vivien E.; Wilson, John; Cemazar, Maja; Shan, Siqing; Dewhirst, Mark W.; Barber, Paul R.; Vojnovic, Borivoj; Chaplin, David J.
CS Gray Cancer Institute, Mount Vernon Hospital, Northwood, HA6 2JR, UK
SO Cancer Research (2001), 61(17), 6413-6422
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS
AN 2000:717223 CAPLUS
DN 134:216909
TI Determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide
AU Parkins, C. S.; Holder, A. L.; Hill, S. A.; Chaplin, D. J.; Tozer, G. M.
CS Tumour Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, HA6 2JR, UK
SO British Journal of Cancer (2000), 83(6), 811-816
CODEN: BJCAAI; ISSN: 0007-0920
PB Harcourt Publishers Ltd.
DT Journal
LA English
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2002 ACS
AN 1999:241795 CAPLUS
DN 131:39356
TI Combretastatin A-4 phosphate as a tumor vascular-targeting agent: early effects in tumors and normal tissues
AU Tozer, Gillian M.; Prise, Vivien E.; Wilson, John; Locke, Rosalind J.; Vojnovic, Borivoj; Stratford, Michael R. L.; Dennis, Madeleine F.; Chaplin, David J.
CS Tumor Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, HA6 2JR, UK
SO Cancer Res. (1999), 59(7), 1626-1634
CODEN: CNREA8; ISSN: 0008-5472
PB AACR Subscription Office
DT Journal
LA English
RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS
AN 2000:717223 CAPLUS
DN 134:216909
TI Determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide
AU Parkins, C. S.; Holder, A. L.; Hill, S. A.; Chaplin, D. J.; Tozer, G. M.
CS Tumour Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, HA6 2JR, UK
SO British Journal of Cancer (2000), 83(6), 811-816
CODEN: BJCAAI; ISSN: 0007-0920
PB Harcourt Publishers Ltd.
DT Journal
LA English
CC 1-6 (Pharmacology)
AB The anti-vascular action of the tubulin binding agent combretastatin A-4 phosphate (CA-4-P) has been quantified in two types of murine tumor, the breast adenocarcinoma CaNT and the round cell sarcoma SaS. The functional vascular vol., assessed using a fluorescent carbocyanine dye, was significantly reduced at 18 h after CA-4-P treatment in both tumor types, although the degree of redn. was very different in the two tumors. The SaS tumor, which has a higher nitric oxide synthase (NOS) activity than the CaNT tumor, showed .apprx.10-fold greater resistance to vascular damage by CA-4-P. This is consistent with our previous findings, which showed that NO exerts a protective action against this drug. Simultaneous administration of CA-4-P with a NOS inhibitor, N.omega.-nitro-L-arginine (L-NNA), resulted in enhanced vascular damage and cytotoxicity in both tumor types.

Administration of diethylamine NO, an NO donor, conferred protection against the vascular damaging effects. Following treatment with CA-4-P, neutrophil infiltration into the tumors, measured by myeloperoxidase (MPO) activity, was significantly increased. Levels of MPO activity also correlated with the levels of vascular injury and cytotoxicity measured in both tumor types. Neutrophilic MPO generates free radicals and may therefore contribute to the vascular damage assocd. with CA-4-P treatment. MPO activity was significantly increased in the presence of L-NNA, suggesting that the protective effect of NO against CA-4-P-induced vascular injury may be, at least partially, mediated by limiting neutrophil infiltration. The data are consistent with the hypothesis that neutrophil action contributes to vascular injury by CA-4-P and that NO generation acts to protect the tumor vasculature against CA4-P-induced injury. The protective effect of NO is probably assocd. with an anti-neutrophil action.

ST antitumor combretastatin A4 phosphate angiogenesis inhibitor nitric oxide

IT Drug resistance
(antitumor; determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide)

IT Angiogenesis inhibitors
(determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide)

IT Neutrophil
(infiltration; determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide)

IT Antitumor agents
(resistance to; determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide)

IT 168555-66-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide)

IT 125978-95-2, Nitric oxide synthase
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide)

IT 10102-43-9, Nitric oxide, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide)

RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Anderson, R; Br J Cancer 1989, V60, P193 CAPLUS
(2) Chalkley, H; J Natl Cancer Inst 1943, V4, P47
(3) Chaplin, D; Anticancer Res 1999, V19, P189 CAPLUS
(4) Chaplin, D; Br J Cancer 1996, V74, PS86 CAPLUS
(5) Dark, G; Cancer Res 1997, V57, P1829 CAPLUS
(6) Eiserich, J; J Biol Chem 1996, V271, P19199 CAPLUS
(7) Eiserich, J; Nature 1998, V391, P393 CAPLUS
(8) Eiserich, J; Proc Natl Acad Sci USA 1999, V96, P6365 CAPLUS
(9) Folkman, J; J Natl Cancer Inst 1990, V82, P4 MEDLINE
(10) Grisham, M; Am J Physiol 1986, V251, PG567 CAPLUS
(11) Grosios, K; Br J Cancer 1999, V81, P1318 CAPLUS
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YOU HAVE REQUESTED DATA FROM FILE 'CAPLUS' - CONTINUE? (Y)/N:y

L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
AN 2001:659027 CAPLUS

DN 136:295

TI Mechanisms associated with tumor vascular shut-down induced by combretastatin A-4 phosphate: intravital microscopy and measurement of vascular permeability

AU Tozer, Gillian M.; Prise, Vivien E.; Wilson, John; Cemazar, Maja; Shan, Siqing; Dewhirst, Mark W.; Barber, Paul R.; Vojnovic, Borivoj; Chaplin, David J.

CS Gray Cancer Institute, Mount Vernon Hospital, Northwood, HA6 2JR, UK

SO Cancer Research (2001), 61(17), 6413-6422
CODEN: CNREA8; ISSN: 0008-5472

PB American Association for Cancer Research

DT Journal

LA English

CC 1-6 (Pharmacology)

AB The tumor vascular effects of the tubulin destabilizing agent disodium combretastatin A-4 3-O-phosphate (CA-4-P) were investigated in the rat P22 tumor growing in a dorsal skin flap window chamber implanted into BD9 rats. CA-4-P is in clin. trial as a tumor vascular targeting agent. In animal tumors, it can cause the shut-down of blood flow, leading to extensive tumor cell necrosis. However, the mechanisms leading to vascular shut-down are still unknown. Tumor vascular effects were visualized and monitored online before and after the administration of two doses of CA-4-P (30 and 100 mg/kg) using intravital microscopy. The combined effect of CA-4-P and systemic nitric oxide synthase (NOS) inhibition using N.omega.-nitro-L-arginine (L-NNA) was also assessed, because this combination has been shown previously to have a potentiating effect. The early effect of CA-4-P on tumor vascular permeability to albumin was detd. to assess whether this could be involved in the mechanism of action of the drug. Tumor blood flow redn. was extremely rapid after CA-4-P treatment, with red cell velocity decreasing throughout the observation period and dropping to <5% of the starting value by 1 h. NOS inhibition alone caused a 50% decrease in red cell velocity, and the combined treatment of CA-4-P and NOS inhibition was approx. additive. The mechanism of blood flow redn. was very different for NOS inhibition and CA-4-P. That of NOS inhibition could be explained by a decrease in vessel diam., which was most profound on the arteriolar side of the tumor circulation. In contrast, the effects of CA-4-P resembled an acute inflammatory reaction resulting in a visible loss of a large proportion of the smallest blood vessels. There was some return of visible vasculature at 1 h after treatment, but the blood in these vessels was static or nearly so, and many of the vessels were distended. The hematocrit within larger draining tumor venules tended to increase at early times after CA-4-P, suggesting fluid loss from the blood. The stacking of red cells to form rouleaux was also a common feature, coincident with slowing of blood flow; and these two factors would lead to an increase in viscous resistance to blood flow. Tumor vascular

permeability to albumin was increased to .apprx.160% of control values at 1 and 10 min after treatment. This could lead to an early decrease in tumor blood flow via an imbalance between intravascular and tissue pressures and/or an increase in blood viscosity as a result of increased hematocrit. These results suggest a mechanism of action of CA-4-P in vivo. Combination of CA-4-P with a NOS inhibitor has an additive effect, which it may be possible to exploit therapeutically.

ST vessel shut combretastatin A4 phosphate intravital permeability

IT Drug interactions
(additive; mechanisms assocd. with tumor vascular shut-down induced by combretastatin A-4 phosphate)

IT Circulation
Hematocrit
(mechanisms assocd. with tumor vascular shut-down induced by combretastatin A-4 phosphate)

IT Blood vessel
(permeability; mechanisms assocd. with tumor vascular shut-down induced by combretastatin A-4 phosphate)

IT Biological transport
(permeation, vascular; mechanisms assocd. with tumor vascular shut-down induced by combretastatin A-4 phosphate)

IT 125978-95-2, NO synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mechanisms assocd. with tumor vascular shut-down induced by combretastatin A-4 phosphate)

IT 168555-66-6
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanisms assocd. with tumor vascular shut-down induced by combretastatin A-4 phosphate)

IT 2149-70-4, Nitro-arginine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanisms assocd. with tumor vascular shut-down induced by combretastatin A-4 phosphate)

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L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2002 ACS
AN 1999:241795 CAPLUS
DN 131:39356
TI Combretastatin A-4 phosphate as a tumor vascular-targeting agent: early effects in tumors and normal tissues
AU Tozer, Gillian M.; Prise, Vivien E.; Wilson, John; Locke, Rosalind J.; Vojnovic, Borivoj; Stratford, Michael R. L.; Dennis, Madeleine F.; Chaplin, David J.
CS Tumor Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, HA6 2JR, UK
SO Cancer Res. (1999), 59(7), 1626-1634

CODEN: CNREA8; ISSN: 0008-5472
PB AACR Subscription Office
DT Journal
LA English
CC 1-6 (Pharmacology)
AB The potential for tumor vascular-targeting by using the tubulin destabilizing agent disodium combretastatin A-4 3-0-phosphate (CA-4-P) was assessed in a rat system. This approach aims to shut down the established tumor vasculature, leading to the development of extensive tumor cell necrosis. The early vascular effects of CA-4-P were assessed in the s.c. implanted P22 carcinosarcoma and in a range of normal tissues. Blood flow was measured by the uptake of radiolabeled iodoantipyrine, and quant. autoradiog. was used to measure spatial heterogeneity of blood flow in tumor sections. CA-4-P (100 mg/kg i.p.) caused a significant increase in mean arterial blood pressure at 1 and 6 h after treatment and a very large decrease in tumor blood flow, which-by 6 h-was reduced approx. 100-fold. The spleen was the most affected normal tissue with a 7-fold redn. in blood flow at 6 h. Calcns. of vascular resistance revealed some vascular changes in the heart and kidney for which there were no significant changes in blood flow. Quant. autoradiog. showed that CA-4-P increased the spatial heterogeneity in tumor blood flow. The drug affected peripheral tumor regions less than central regions. Administration of CA-4-P (30 mg/kg) in the presence of the nitric oxide synthase inhibitor, N.omega.-nitro-L-arginine Me ester, potentiated the effect of CA-4-P in tumor tissue. The combination increased tumor vascular resistance 300-fold compared with less than 7-fold for any of the normal tissues. This shows that tissue prodn. of nitric oxide protects against the damaging vascular effects of CA-4-P. Significant changes in tumor vascular resistance could also be obtained in isolated tumor perfusions using a cell-free perfusate, although the changes were much less than those obsd. in vivo. This shows that the action of CA-4-P includes mechanisms other than those involving red cell viscosity, intravascular coagulation, and neutrophil adhesion. The uptake of CA-4-P and combretastatin A-4 (CA-4) was more efficient in tumor than in skeletal muscle tissue and dephosphorylation of CA-4-P to CA-4 was faster in the former. These results are promising for the use of CA-4-P as a tumor vascular-targeting agent.
ST antitumor antiangiogenic combretastatin A4 phosphate NO
IT Angiogenesis inhibitors
Antitumor agents
Blood vessel
Circulation
(combretastatin A-4 phosphate as a tumor vascular-targeting agent)
IT 117048-59-6, Combretastatin A-4 168555-66-6
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or

effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(combretastatin A-4 phosphate as a tumor vascular-targeting agent)

IT 50903-99-6, N.omega.-Nitro-L-arginine methyl ester
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(combretastatin A-4 phosphate as a tumor vascular-targeting agent)

IT 10102-43-9, Nitric oxide, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(combretastatin A-4 phosphate as a tumor vascular-targeting agent)

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ANSWER 65 OF 69 CAPLUS COPYRIGHT 2002 ACS
AN 1995:563071 CAPLUS
DN 123:25428
TI S-alkyl-L-thiocitrullines. Potent stereoselective inhibitors of nitric oxide synthase with strong pressor activity in vivo
AU Narayanan, Krishnaswamy; Spack, Larry; McMillan, Kirk; Kilbourn, Robert G.; Hayward, Michael A.; Masters, Bettie Sue Siler; Griffith, Owen W.
CS Departments of Biochemistry and Pediatrics, Medical College of Wisconsin, Milwaukee, WI, 53226, USA
SO J. Biol. Chem. (1995), 270(19), 11103-10
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
CC 1-8 (Pharmacology)
AB Nitric oxide synthase catalyzes the oxidn. of a guanidino nitrogen of L-arginine to nitric oxide with concomitant formation of citrulline. Enzyme activity is inhibited by a variety of N.omega.-monosubstituted L-arginine analogs including N.omega.-alkyl-, N.omega.-amino-, and N.omega.-nitro-L-arginine derivs. The authors report here that both constitutive and inducible isoforms of nitric oxide synthase are strongly inhibited by S-alkyl-L-thiocitrullines (N.delta.-(S-alkyl)isothioureido-L-ornithines) with n-alkyl groups of one to three carbons. These compds. represent a novel class of inhibitors and are the most potent nitric oxide synthase-inhibiting amino acids described to date. Inhibition is reversible, stereoselective, and competitive with L-arginine. Spectral studies show no direct interaction of inhibitor sulfur with heme iron, a result in contrast to that seen previously with the parent compd., L-thiocitrulline. The S-alkyl-L-thiocitrullines have strong pressor activity in normotensive control rats; S-methyl-L-thiocitrulline reverses hypotension in a rat model of septic peritonitis and in dogs administered endotoxin. These latter findings suggest that the inhibitors may have therapeutic utility in treating hypotension due to the overprodn. of nitric oxide.
ST alkylthiocitrulline nitric oxide synthase inhibitor antihypotensive
IT Antihypotensives
Kinetics, enzymic
(alkylthiocitrullines as potent stereoselective inhibitors of nitric oxide synthase with strong pressor activity in vivo)
IT Molecular structure-biological activity relationship
(nitric oxide synthase-inhibiting; alkylthiocitrullines as potent stereoselective inhibitors of nitric oxide synthase with strong pressor activity in vivo)
IT 158875-72-0P, S-Ethyl-L-thiocitrulline 160203-44-1P 164228-82-4P 164228-83-5P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(alkylthiocitrullines as potent stereoselective inhibitors of nitric oxide synthase with strong pressor activity in vivo)

IT 156719-39-0 164228-81-3
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkylthiocitrullines as potent stereoselective inhibitors of nitric oxide synthase with strong pressor activity in vivo)

IT 125978-95-2, Nitric oxide synthase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(alkylthiocitrullines as potent stereoselective inhibitors of nitric oxide synthase with strong pressor activity in vivo)

L1 ANSWER 68 OF 70 CAPLUS COPYRIGHT 2002 ACS

AN 1996:7152 CAPLUS

DN 124:106558

TI L-N6-(1-Iminoethyl)-lysine
potently inhibits inducible nitric oxide synthase and is superior to NG-monomethyl-arginine in vitro and in vivo

AU Stenger, Steffen; Thuering, Heike; Roellinghoff, Martin; Manning, Pamela; Bogdan, Christian

CS Institute of Clinical Microbiology and Immunology, University of Erlangen, Erlangen, Germany

SO Eur. J. Pharmacol. (1995), 294(2/3), 703-12
CODEN: EJPHAZ; ISSN: 0014-2999

DT Journal

LA English

CC 1-12 (Pharmacology)
Section cross-reference(s): 13

AB L-N6-(1-Iminoethyl)-lysine
is a novel inhibitor of nitric oxide (NO) synthase, which similar to aminoguanidine but unlike NG-monomethyl-L-arginine is 30-fold more selective for the inducible than for the constitutive isoform of the enzyme. Here, the authors characterized this inhibitor for the first time in intact cells and during infection of mice with a NO-sensitive parasite (Leishmania major). L-N6-(1-Iminoethyl)-lysine potently inhibited the activity of inducible NO-synthase in primary macrophages. After stimulation by interferon-.gamma., the IC50 of L-N6-(1-iminoethyl)-lysine was 0.4 .mu.M and 10- or 30-fold lower than that of NG-monomethyl-L-arginine or aminoguanidine, resp. In vivo, L-N6-(1-iminoethyl)-lysine (0.4-9 mM in the drinking water) suppressed inducible NO-synthase activity and caused a dramatic exacerbation of leishmaniasis, despite a counterregulatory increase of inducible NO-synthase protein in the tissue. In contrast, considerably higher concns. of

NG-monomethyl-L-arginine (20-50 mM) were required to achieve comparable effects. NG-Monomethyl-L-arginine, but not L-N6-(1-iminoethyl)-lysine led to wt. loss, reduced water and food consumption. The authors conclude that L-N6-(1-iminoethyl)-lysine should be used instead of NG-monomethyl-L-arginine for potent suppression of inducible NO-synthase in vitro and in vivo.

ST iminoethyllysine inducible nitric oxide synthase inhibitor; methylarginine inducible nitric oxide synthase inhibitor; lysine deriv nitric oxide synthase inhibitor

IT Leishmania major
(infection with; (iminoethyl)lysine potently inhibits inducible nitric oxide synthase and is superior to methylarginine in vitro and in vivo in relation to leishmaniasis)

IT 17035-90-4, NG-Monomethyl-arginine 53774-63-3
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
((iminoethyl)lysine potently inhibits inducible nitric oxide synthase and is superior to methylarginine in vitro and in vivo in relation to leishmaniasis)

IT 125978-95-2, Nitric oxide synthase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
((iminoethyl)lysine potently inhibits inducible nitric oxide synthase and is superior to methylarginine in vitro and in vivo in relation to leishmaniasis)